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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,132	10/17/2003	Avi J. Ashkenazi	P1134R2C4	2023

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/688,132	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65 and 67-93* is/are pending in the application.

4a) Of the above claim(s) *65 and 77-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *65 and 67-93* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/22/06,4/18/06,5/5/04,3/15/04.

DETAILED ACTION

Election/Restrictions

Applicant's election of the species of treatment of an inflammatory disease or disorder (including inflammation) in the reply filed on Nov. 22, 2006, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 67-76 read on the elected species and are here examination.

Sequences

When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02. In the instant application, a sequence identifier must be used for the sequences appearing in Figures 1, 2, 5 and 6.

Appropriate correction is required.

Specification

The disclosure is objected to because of the following informalities: There are blanks instead of ATCC accession numbers and dates listed on page 51, and there are blanks for ATCC accession numbers on page 27, lines 37-38 and 41.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn broadly to methods of treating or preventing inflammation or an inflammatory disease or disorder. The claims are not enabled for two reasons. The first minor reasons is that it appears the methods claimed are supposed to function by having DcR3 bind FasL, since FasL was known to be involved in inflammation. However, the claims encompass a polypeptide comprising only resides 24-215 of SEQ ID NO:1 (DcR3). Wrobleweski et al. (Biochem. Pharmacol., 65 :657, 2003) show that a DcR3 fragment comprising 1-218 had greatly reduced binding Fas L and inhibition of FasL-mediated apoptosis of Jurkat cells *in vitro* compared to untruncated DcR3 and was not able to block sFasL-mediate apoptosis (p. 622, section 3.3, and Fig. 6A). They found "DcR3 (1-218) did not bind FasL or inhibit FasL-mediated apoptosis, but maintained its ability to bind LIGHT and interrupt activities mediated through this ligand binding pathway (p. 665, col, 1, 7 lines from bottom). The specification shows only full or mature DcR3 has the ability to block FasL-induced apoptosis (Example 10). There is no showing of a truncated form having that ability. Therefore, even assuming the method was enabled for using DcR3, (which as discussed immediately below, it is not agreed that it is) a polypeptide that did not comprise at least amino acids 24-300 or SEQ ID NO:1 would not be.

The second reason the invention is not enabled is that the role of FasL, let alone the role of DcR3, in inflammation is complicated, dependent on the activity of other molecules and unpredictable so it would require undue experimentation for the the skilled artisan to use the invention as claimed. The specification does not provide information about how to use DcR3, but suggests that the role of FasL is to reduce inflammation by inducing apoptosis (paragraph beginning at the end of page 1 of the specification). Without further information, one would conclude that administration of DcR3, which would bind FasL and prevent it from binding and activating the Fas receptor, would lead to inhibition of FasL-induced apoptosis and would actually result in increased inflammation.

There are many conflicting examples of the role of FasL in the induction of inflammation. For example, in experiments comparing mice with or without functional FasL, mice injected with bacterial pneumococcal meningitis showed no difference in pathophysiology

between wildtype and deficient mice (*e.g.*, Fig. 2 and p. 81, second to last sentence, Paul et al., J. Neuroimmunol. 152:78, 2004), suggesting that FasL was not involved in the bacterial meningitis inflammatory response. On the other hand, when the mice were injected with the Lyme disease bacteria B. *burgdorferi*, the FasL deficient mice had significantly less arthritis, suggesting that FasL stimulates inflammation in response to the Lyme bacteria (*e.g.*, TABLE 1, p. 1158, col. 2, last paragraph, Shi et al., Infect. Immunity, 74(2):1156, 2006). Maher et al. (Immnol., Cell Biol. 80:131, 2002), Whiteside (Seminars Cancer Biol. 12:43, 2002) and Lamhamedi-Cherradi et al. (J. Clin. Immunol. 21(1):24, 2001) reviewed experimental results designed to elucidate the role of FasL in inflammation. Maher et al. concluded (p. 135, col. 2, third full paragraph) that "It may be that the actions of FasL are dependent simply on the type of tissue that expresses it; the sensitivity of the cell, whether normal or neoplastic, to Fas-FasL-mediated cell death; and, importantly, the cytokine milieu in which the signals are delivered." Similarly, Whiteside states (p. 47, col.2, approximately 2/3 down), "Apparently, cytokines present in the tumor or tissue microenvironment can regulate pro-inflammatory *versus* immunosuppressive activity of FasL. At the immune privileged sites, where the cytokine microenvironment is anti-inflammatory, immunosuppressive effects of FasL may be favored, while its pro-inflammatory activity may be suppressed. Thus, regulation of FasL activities is directed, at last in part, by cytokines in the environmental context." Lamhamedi-Cherradi in discussing FasL gene transfer experiments notes (p. 25, col., 1 second full paragraph) that "While transgenic expression of FasL in the inflamed joints, certain tumors, and transplants conferred immune privilege, FasL expression in pancreatic islets and some other tumors or transplants caused tissue injury and induced inflammation." Even in the simplest view of FasL as inducing apoptosis and inhibiting inflammation, administration of DcR3 would have the opposite effect on inflammation by reducing apoptosis and not be useful for the claimed method. Nevertheless, the art shows that action of FasL is far more complex and, for the reasons above, inhibiting the action of FasL would cause unpredictable effects on inflammation or inflammatory diseases or disorders and could not be used to treat or prevent such.

Priority

It is also noted that while provisional priority application US 60/059,288 discloses the complete DcR3 protein and encoding nucleic acid sequences, it does not disclose a specific utility for the protein. It is disclosed only that the protein is related to TNFR2, but no specific ligand is identified. Therefore, US 60/059,288 cannot support the currently claimed methods and the instant application is not granted benefit of priority to US 60/059,288. For the sake of prior art, the effective filing date of the instant application is that of US 60/094,640, filed 07/30/98.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67, 68 and 71-74 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 5,885,800 (Emery et al cited by Applicants).

US Patent 5,885,800 teaches the TR4 polypeptide (SEQ ID NO:2) which has a sequence identical to the DcR3 polypeptide (SEQ ID NO:1) of the instant application. Treating inflammation, inflammatory bowel disease and psoriasis using TR4 is also taught. Because treatment is also directed to Alzheimers disease and AIDS, subjects to be treated necessarily include humans.

Claims 67-76 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2002/0150583 (Gentz et al., cited by applicants).

US 2002/0150583 teaches TNFR-6α polypeptide (TR6, SEQ ID NO:2) which has the same sequence as DcR3 (SEQ ID NO:1) of the instant application. Also, taught is the use of disclosed polypeptides for the treatment of patients including humans (middle of [0386]). Treatment of inflammation and inflammatory diseases or disorders by administering TNFR-6α polypeptide is disclosed, including inflammatory bowel disease ([0460]) and psoriasis ([0457]). Also taught is TNFR-6α polypeptide fused to an immunoglobulin constant region (Fc) to treat or prevent diseases or conditions associated with inflammation ([0458]).

It is noted that US 2002/0150583 (Gentz et al.) receives an effective filing date which is the filing date of provisional application US 60/035,496, filed January 14, 1997. The provisional teaches that HIV-induced apoptosis can be treated with an antagonist of the invention (paragraph bridging pages 55-56), and that an antagonist can be a soluble form of the receptor (page 54, lines 28-30). Badley et al., submitted in the response filed April 25, 1996 in US 2002/0150583, demonstrates that FasL mediates HIV-induced apoptosis, and that an antagonist to FasL abrogates the HIV-infected macrophage-dependent death of T lymphocytes. US 60/035,496 also discloses treatment of inflammatory bowel disease (bottom of p. 56).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

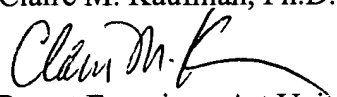
Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

February 6, 2007